Ann Surg Oncol (2025) 32:6467–6476
https://doi.org/10.1245/s10434-025-17736-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

REVIEW ARTICLE – PANCREATIC TUMORS

The Landmark Series: Neoadjuvant Therapy for Resectable Pancreatic Cancer

Chelsea F. Cardell, MD[1], Esther N. Dekker, MD[1,2], Matthew H. G. Katz, MD[1], and Ching-Wei D. Tzeng, MD[1]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Department of Surgery, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

ABSTRACT Pancreatic ductal adenocarcinoma (PDAC) remains a malignancy with limited 5-year overall survival, but recent advances in maximizing chemotherapy delivery has offered some improvement across all stages. Delivery of induction chemotherapy for localized PDAC has several putative benefits, including early treatment of occult metastases, pragmatically ensuring all patients receive systemic therapy, and improved R0 resection rates. While neoadjuvant therapy has become widely accepted in borderline resectable clinical stage, its role in patients with resectable disease is less clear. This Landmark Series article discusses key studies informing the ongoing debate about neoadjuvant therapy for resectable PDAC, both published and ongoing.

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease with a 5-year overall survival (OS) that has slowly risen from low single digits to 13% with the increasing use of systemic triplet and double therapies.[1] Widely recognized as a systemic disease even when "localized" radiographically, PDAC treatment requires a multimodal approach in which both surgical resection and systemic chemotherapy are considered fundamental cornerstones of management.[2,3] Historically, usual care for anatomically resectable PDAC included upfront surgery followed by intended adjuvant chemotherapy.[4] Current guidelines have expanded those recommendations to include either upfront surgery (with intended adjuvant therapy) or neoadjuvant therapy (NT) followed by resection, with the choice influenced by the presence or not of high-risk "borderline" anatomic features such as large tumor size; biologic features such as clinical node positivity, indeterminate nodules with suspicion for metastatic disease, and/or markedly elevated carbohydrate antigen 19-9 (CA19-9) levels; and conditions including reduced performance status and comorbidities.[5–7]

Proponents of NT for resectable PDAC argue for the potential to treat occult micrometastatic disease and universally treat all patients thought to have localized disease with systemic chemotherapy.[8] This is also a pragmatic approach that takes into consideration that less than half of Americans get a single meaningful dose of adjuvant therapy after pancreatectomy. Even in randomized trials of highly selected patients, the postoperative completion (or even initiation) rate of adjuvant therapy is far from universal. Additionally, major surgical complications have a greater negative effect on chemo-naïve patients than those who have completed induction chemo and resection already by delaying their first dose of chemotherapy. The preoperative window also offers the ability to evaluate both standard cytotoxic and novel therapeutic agents targeting the in situ tumor microenvironment, an approach not feasible in the postoperative setting.

While the induction chemotherapy period allows the declaration of rapidly progressive disease inappropriate for a major operation and may facilitate microscopically complete (R0) surgical resection by reducing tumor size,[9] there remains a major argument by critics of NT who state that patients miss their window for surgery.

While there are many retrospective cohort studies stating the survival advantages of NT, those who remain skeptical of NT advocate for definitive prospective evidence before

Chelsea F. Cardell and Esther N. Dekker have shared first authorship.

First Received: 4 June 2025
Accepted: 9 June 2025
Published online: 7 July 2025

C.-W. D. Tzeng, MD
e-mail: CDTzeng@mdanderson.org

shifting treatment toward the generally accepted paradigm in borderline resectable PDAC, where induction chemotherapy is now usual care.

To date, conclusive evidence demonstrating a survival advantage of neoadjuvant therapy in resectable PDAC remains limited. Despite theoretical benefits, the efficacy of neoadjuvant therapy in terms of OS continues to be a subject of debate and ongoing research. In this article, we review the landmark clinical trials and retrospective data that provide evidence for the use of NT in patients with resectable PDAC.

PUBLISHED NEOADJUVANT TRIALS

A landmark review by Patel et al. provided a comprehensive overview of preoperative therapy for PDAC.[10] The authors highlighted the rationale, historical context, and key clinical trials that have informed clinical practice guidelines for resectable and borderline resectable PDAC. Table 1 provides an updated overview of published phase II/III RCTs with key trials discussed in greater detail below.

NORPACT-1

Purpose the objective of this study was to evaluate the efficacy and safety of neoadjuvant fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) versus upfront surgery in patients with resectable PDAC of the head.[11] This investigation expanded on findings of improved OS of patients receiving adjuvant FOLFIRINOX by assessing the potential benefits of FOLFIRINOX in a neoadjuvant setting.

Study design this trial was a multicenter, randomized, phase II study conducted across 12 hospitals in four countries in Scandinavia. Eligible patients had performance status of 0–1 and resectable PDAC. Patients were randomized to 4 cycles of neoadjuvant FOLFIRINOX, followed by surgery with 8 intended cycles of adjuvant therapy, or to upfront surgery followed by 12 planned cycles of adjuvant therapy. The primary endpoint was OS at 18 months. The FOLFIRINOX dose was the same as in previous publications without mention of allowances for real-world dose reductions.

Results this trial randomized 140 patients, with 77 assigned to neoadjuvant FOLFIRINOX and 63 to adjuvant FOLFIRINOX (2017–2021). In the intention-to-treat analysis, the 18-month survival rate was 60% (95% confidence intervals (CI) 49–71) for neoadjuvant FOLFIRINOX versus 73% (62–84) for upfront surgery ($p = 0.032$). Median overall survival was 25.1 months (95% CI 17.2–34.9) for neoadjuvant FOLFIRINOX compared with 38.5 months (95% CI 27.6–not reached) for adjuvant FOLFIRINOX (HR 1.52 [95% CI 1.00–2.33], $p = 0.050$). The per-protocol analysis showed similar trends. Resection rates were comparable between groups (82% versus 89%, $p = 0.24$). Adjuvant chemotherapy initiation rates were similar (86% versus 90%, $p = 0.56$).

Conclusion of the study this study showed no survival benefit for neoadjuvant FOLFIRINOX compared with upfront surgery in patients with resectable PDAC and reaffirmed upfront surgery as the standard of care.

Commentary this was the first published phase II RCT to compare neoadjuvant FOLFIRINOX versus upfront surgery in patients with resectable PDAC and demonstrated no survival benefit for neoadjuvant FOLFIRINOX compared with upfront surgery. On the contrary, it suggested a detrimental effect of using induction triplet therapy in their study population. The study's outcomes were potentially influenced by suboptimal implementation of protocolized induction chemotherapy dosages, as only 46% of the patients received even four scheduled preoperative cycles. This would be mitigated in real practice, where dose reductions are normal, and thus is highly probable to have affected the 18-month outcomes. In addition, 13 of 77 patients in the neoadjuvant arm did not even receive one cycle because 10 of them would never have qualified for neoadjuvant therapy in real-life (no diagnosis, wrong diagnosis, and unfixable bilirubin). Furthermore, while neoadjuvant duration of up to 4–6 months is often used in real world practice, the NORPACT-1 trial employed a shorter 2-month neoadjuvant protocol, which also may have significantly influenced both treatment effectiveness and time of medical optimization. The NORPACT trial OS results were unexpected to proponents of NT and perhaps generated more questions than answers, but does highlight a valid criticism of NT, being that careful implementation of induction chemotherapy is needed, including dosing and closely monitoring patients, to avoid falling off the neoadjuvant pathway.

PANACHE01-PRODIGE48

Purpose the objective of this study was to evaluate the feasibility, safety, and efficacy of neoadjuvant modified (m) FOLFIRINOX in patients with resectable PDAC.[12]

Study design the PANACHE/Prodige48 trial was a multicenter phase II randomized trial conducted in 28 centers in France. Patients were randomized in a 2:2:1 ratio to receive either four biweekly cycles of mFOLFIRINOX (arm 1), leucovorin, fluorouracil, and oxaliplatin [FOLFOX] (arm 2) both followed by surgery, and adjuvant 4 months of chemotherapy or upfront surgery followed by 6 months of adjuvant chemotherapy (control arm). The primary endpoints were the 1-year OS rate and the completion rate of the intended treatment protocol.

Results between 2017 and 2020, 153 patients were randomized to arm 1 ($n = 72$), arm 2 ($n = 50$), and the control arm ($n = 31$). The median OS was 31.3 months (90% CI 21.5–not reached) in the FOLFIRINOX arm and 31.8

TABLE 1 Published phase II/III randomized controlled trials investigating neoadjuvant therapy in patients with PDAC

Trial	Country	Intervention	Comparator	Resectability status	Primary outcome	Sample size	Enrollment period	Median OS, months
Palmer et al. [24]	UK	Neoadjuvant gemcitabine and cisplatin followed by surgery	Neoadjuvant gemcitabine (every 7 days for 43 days) followed by surgery	Resectable	Resection rate	50	1999–2003	15.6 (95% CI 10.1-24.2) versus 9.9 (95% CI 8.5-24.2)
Golcher et al.[a] [25]	Germany	Neoadjuvant gemcitabine and cisplatin (four doses) with radiotherapy (1.8–55.8 or 50.4 Gy) followed by surgery and adjuvant gemcitabine	Upfront surgery with adjuvant gemcitabine (six cycles)	Resectable	OS	73	2003–2009	17.4 versus 14.4 (p = 0.96)
Casadi et al.[a] [26]	Italy	Neoadjuvant gemcitabine with radiotherapy (two cycles; 45 Gy + 9 Gy followed by surgery	Upfront surgery	Resectable	R0 resection	38	2007–2014	22.4 versus 28.2
PACT-15 [27] Phase II/III	Italy	Neoadjuvant PEXG (three cycles) followed by surgery and adjuvant PEXG (three cycles)	Upfront surgery with adjuvant gemcitabine (six cycles) or PEXG (six cycles)	Resectable	1-year event-free survival	93	2010–2015	38.2 (27.3–49.1) versus 20.4 (95% CI 14.6–25.8) versus 26.4 (95% CI 15.8–26.7)
Prep 02/JSAP-05 [15] Phase III	Japan	Neoadjuvant gemcitabine and S-1 (two cycles) followed by surgery and adjuvant S-1 (four cycles)	Upfront surgery with adjuvant S-1 (four cycles)	Resectable. Borderline-resectable NCCN	OS	364	2013–2016	37.0 (28.6-43.3) versus 26.6 (21.5-31.5); HR 0.73 [95% CI 0.56-0.95, p = 0.018]
PREOPANC [28] Phase III	The Netherlands	Neoadjuvant gemcitabine with radiotherapy (three cycles; 36 Gy in 15 fractions) followed by surgery and adjuvant gemcitabine (four cycles)	Upfront surgery with adjuvant gemcitabine (six cycles)	Resectable. Borderline-resectable DPCG	OS	246	2013–2017	15.7 (95% CI 12.9-20.6) versus 14.3 (95% CI, 12.7-17.9); HR 0.73 (95% CI 0.56- 0.96, p = 0.025)

Table 1 (continued)

Trial	Country	Intervention	Comparator	Resectability status	Primary outcome	Sample size	Enrollment period	Median OS, months
SWOG S1505 [13] Phase II	USA	Neoadjuvant mFOLFIRINOX (three cycles) followed by surgery and adjuvant mFOLFIRINOX (three cycles)	Neoadjuvant gemcitabine and Abraxane (three cycles) followed by surgery and adjuvant gemcitabine and Abraxane (three cycles)	Resectable NCCN	2-year OS	147	2015–2018	23.2 (95% CI 17.6-45.9) versus 23.6 (95% CI 17.8-31.7)
NEONAX -AIO-PAK-0313 [14] Phase II	Germany	Neoadjuvant gemcitabine and Abraxane (two cycles) followed by surgery and adjuvant gemcitabine and Abraxane (four cycles)	Upfront surgery with adjuvant gemcitabine and Abraxane (six cycles)	Resectable NCCN	18-month DFS	127	2015–2019	25.5 (95% CI 19.7-29.7) versus 16.7 (95% CI 11.6-22.2 months)
PANACHE01-PRODIGE48 [12] Phase II	France	Neoadjuvant mFOLFIRINOX or FOLFOX (four cycles) followed by surgery and adjuvant chemotherapy (4 months)	Upfront surgery with adjuvant chemotherapy (6 months)	Resectable NCCN	1-year OS	153	2017–2020	31.3 (90% CI 21.5-not reached) versus 31.8 (90% CI 23.8-not reached) versus control arm: median not reached (90% CI 18.5-not reached)
PREOPANC-2[b] [16] Phase III	The Netherlands	Neoadjuvant FOLFIRINOX (eight cycles) followed by surgery	Neoadjuvant gemcitabine with radiotherapy (three cycles; 36 Gy in 15 fractions) followed by surgery and adjuvant gemcitabine (four cycles)	Resectable. Borderline-resectable DPCG	OS	375	2018–2021	21.9 versus 21.3; HR 0.87 (95% CI 0.68-1.12, $p = 0.28$)
NORPACT-1 [11] Phase II	Denmark, Finland, Norway, Sweden	Neoadjuvant FOLFIRINOX (four cycles) followed by surgery and adjuvant mFOLFIRINOX (eight cycles)	Upfront surgery with adjuvant mFOLFIRINOX (12 cycles)	Resectable NCCN	18-month OS	140	2017–2021	25.1 (95% CI 17.2–34.9) versus 38.5 (27.6–not reached); HR 1.52 (95% CI 1.00–2.33, $p = 0.050$)

[a]The trial was prematurely terminated owing to insufficient recruitment rates

[b]The full manuscript has not been published as of yet

CI confidence interval, *DFS* disease-free survival, *DPCG* Dutch Pancreatic Cancer Group, *PEXG* cisplatin, epirubicin, capecitabine, gemcitabine, *FOLFIRINOX* fluorouracil, leucovorin, irinotecan, and oxaliplatin, *FOLFOX* fluorouracil, leucovorin, and oxaliplatin, *HR* hazard ratio, *M* modified, *NCCN* National Comprehensive Cancer Network, *OS* overall survival

months (90% CI 23.8–not reached) in the FOLFOX arm. In the control group, median OS was not estimable. The 1-year OS rate was 84.3% (90% CI 75.3–90.9) in arm 1, 71.4% (90% CI 59.0–81.8) in arm 2, and 82.1% (90% CI 71.1–95.0) in the control arm. The rate of patients that completed the therapeutic sequence was 70.8% (90% CI 60.8–79.6) in arm 1 and 68% (90% CI 55.5–78.8) in arm 2. Arm 2 was stopped after interim analysis for lack of efficacy.

Conclusions this study showed that the perioperative administration of mFOLFIRINOX is both feasible and effective.

Commentary although the trial included an upfront surgery control arm, it was designed as a noncomparative randomized phase II study, with primary endpoints evaluated separately in each arm and no formal statistical comparison planned between the groups. As a result, the study provided feasibility and efficacy data, and, while tempting to compare neoadjuvant FOLFIRINOX or FOLFOX with the third arm (upfront surgery), it was not an a priori statistical comparison. Therefore, it did not prove superiority of either regimen over upfront surgery. Additionally, this study also employed a short NT window (2 months), similar to the NORPACT trial.

SWOG S1505

Purpose the aim of this study was to assess feasibility and clinical utility of neoadjuvant and adjuvant chemotherapy using two modern, multiagent chemotherapy regimens in resectable pancreatic cancer. The authors compared the feasibility, safety, and efficacy of mFOLFIRINOX (oxaliplatin, irinotecan, and fluorouracil) with that of gemcitabine/nab-paclitaxel (GA).(13)

Study design this study was a multi-institutional, randomized phase 2 trial conducted through the National Clinical Trials Network with a pick-the-winner design. Inclusion criteria included pathologic diagnosis of PDAC, Zubrod Performance Score of 0 or 1, and determined resectable by central radiology review. Radiologic criteria included no interface of tumor with celiac, common hepatic, or superior mesenteric arteries; < 180° interface between tumor and vessel wall of portal or superior mesenteric veins; patent portal vein/splenic confluence; and absence of metastatic disease (including lymphadenopathy outside the surgical basin). Patients were randomized 1:1 to 12 weeks of mFOLFIRINOX or GA followed by repeat imaging. In the absence of disease progression, patients proceeded to surgical resection within 4–8 weeks following last dose of neoadjuvant chemotherapy. Adjuvant chemo was started 4–12 weeks postop. The primary outcome was 2-year overall survival (OS) from time of randomization with a prespecified threshold of 40%.

Results between 2015 and 2018, 55 patients were randomized to the mFOLFIRINOX arm (arm 1) and 47 to the GA arm (arm 2). In arm 1, 46 (84%) of patients completed neoadjuvant treatment and 40 (73%) underwent resection. In arm 2, 40 (85%) completed neoadjuvant and 33 (70%) underwent resection. Of the patients that underwent resection, 27 in arm 1 (68%, 49% overall) and 19 in arm 2 (58%, 40% overall) completed all treatment. The 2-year OS was 47% (95% CI, 31–61%; $p = 0.15$) in arm 1 and 48% (95% CI, 31–63%; $p = 0.14$), neither of which was higher than the prespecified threshold of 40%. Median survival in arm 1 and 2 was 23.2 (95% CI, 17.6–45.9) and 23.6 (95% CI, 17.8–38.7), respectively.

Conclusions this trial establishes the safety and feasibility of a perioperative approach to chemotherapy but did not demonstrate improved OS with the approach compared with historical data from adjuvant trials.

Commentary this study demonstrated the feasibility of a perioperative approach to chemotherapy across numerous academic and community hospital settings. This trial used the intergroup resectability criteria and highlighted the variability in resectability criteria, with 29% of patients rendered ineligible after post hoc central radiologic review. Additionally, the study demonstrated a reasonable rate (70%) of patients safely reached resection. Less than 50% of patients completed all therapy despite low rates of surgical complications; however, 88% of patients were able to complete neoadjuvant therapy. This improved preoperative delivery rate suggests that a total neoadjuvant approach may improve chemotherapy delivery rates. Finally, although the trial was a simple pick-the-winner decision instead of a formal between-arm comparison of chemotherapy regimens, both mFOLFIRINOX and GA produced similar results.

NEONAX

Purpose this trial examined perioperative versus adjuvant chemotherapy with GA in patients with resectable pancreatic cancer.[14]

Study design this randomized, phase 2 study was conducted across 22 German centers; it randomized patients to two cycles of preoperative GA, surgery, then four cycles of GA within 12 weeks of surgery (arm A) versus upfront surgery with six cycles of postoperative GA (arm B). Patients were considered eligible if they had ECOG status 0 or 1 and had resectable status as defined by clear fat planes around the celiac artery, hepatic artery, and superior mesenteric artery on CT within 4 weeks of randomization. The primary endpoint was disease-free survival (DFS) at 18 months, with a prespecified improvement rate to at least 55%.

Results 127 patients were randomized between 2015 and 2019, with 118 eligible for assessment (59 each arm). A total of 54 patients (92%) in arm A started preoperative

chemo, and 41 (69.5%) underwent resection, with 30 (51%) patients completing adjuvant treatment. In arm B, 42 (78%) patients underwent resection, and 25 (42%) completed adjuvant therapy. R0 resection rate was 87.8% in arm A and 67.4% in arm B. The primary endpoint of DFS of 55% at 18 months was not reached in either arm. Median DFS was 14.1 months (95% CI 10.2–16.8) in arm A and 17 months (95% CI 10.9–25.1) in arm B. OS in the intention-to-treat population was examined as a secondary analysis, with 25.5 months (95% CI 19.7–29.7) in arm A and 16.7 months (95% CI 11.6–22.2) in arm B.

Conclusions this trial demonstrates the safety and feasibility of preoperative chemotherapy. Although the primary endpoint was not reached in either arm, median OS in the intention-to-treat (ITT) population favored the neoadjuvant arm.

Commentary this trial did not reach its primary endpoint or establish superiority of either arm. However, it did highlight improved delivery of chemotherapy in the neoadjuvant arm compared with adjuvant therapy alone. Completion of adjuvant therapy is similar to other trials, with around half of patients failing to complete treatment in either arm. Patients in this trial also received 8 weeks of preoperative chemotherapy followed by 16 weeks of adjuvant, compared with 12 of preoperative and 12 of postoperative as used in SWOG S1505, leading to questions of optional treatment duration.

PREP-02/JSAP-05

Purpose this trial examined neoadjuvant therapy with gemcitabine and S-1 versus upfront surgery for patients with resectable pancreatic cancer.[15]

Study design this trial was a randomized phase II/III trial conducted in 67 Japanese centers. Patients were randomized in a 1:1 ratio to neoadjuvant chemotherapy consisting of gemcitabine (1000 mg/m^2 days 1 and 8) and S-1 (40–60 mg orally twice daily, days 1–14 every 3 weeks for two cycles), followed by surgery and adjuvant four cycles of S-1, or to upfront surgery followed by four cycles of adjuvant S-1. The primary endpoint was resection rate for phase II part of the trial and OS for the phase III part.

Results in total, 364 patients were randomized, 182 patients each to neoadjuvant chemotherapy and upfront surgery, between 2013 and 2016. Median OS was 37.0 months (95% CI 28.6–43.3) in the neoadjuvant gemcitabine and S-1 arm versus 26.6 months (95% CI 21.5–31.5) in the upfront surgery arm; hazard ratio (HR) was 0.73 (95% CI 0.56–0.95; $p = 0.018$). The OS rate at 1, 2, and 3 years was 87.1%, 63.7%, and 50.2%, respectively, in the neoadjuvant chemotherapy arm compared with 75.9%, 52.8%, and 36.6%, respectively, in the upfront surgery arm. The resection rates were 93% in the neoadjuvant gemcitabine and S-1 arm and 82% in the upfront surgery arm. The completion rate of four cycles of S-1 adjuvant therapy was 62.1% in the neoadjuvant chemotherapy arm compared with 63.3% in the upfront surgery arm.

Conclusion the Prep-02/JSAP-05 trial demonstrated that neoadjuvant chemotherapy with gemcitabine and S-1 resulted in improved survival compared with upfront surgery in patients with resectable pancreatic cancer.

Commentary the Prep-02/JSAP05 trial was the first phase III randomized study to demonstrate that neoadjuvant chemotherapy with gemcitabine and S-1 improved OS compared with upfront surgery in patients with resectable PDAC. While these results established gemcitabine and S-1 as an effective neoadjuvant option in Japan and proved the effectiveness of using a neoadjuvant doublet regimen, S-1 is not used outside of East Asia. Therefore, the generalizability of this trial to the Western world remains limited, and the ideal neoadjuvant regimen has yet to be established. Even in this trial of selected patients, the postoperative rate of adjuvant therapy did not quite reach two out of three patients, further highlighting the logistical issues of administration adjuvant therapy in patients as seen in other neoadjuvant trials. In real-world practice, without the resources of a clinical trial, the rate is likely even lower. Including unresected patients, 93% of the neoadjuvant arm received multimodal therapy, while only 52% (63.3% of 82% resected) received complete multimodal therapy.

PRELIMINARY CLINICAL TRIAL RESULTS

A total of three notable clinical trials examining neoadjuvant therapy in pancreatic cancer have reported preliminary findings at meetings but have yet to publish full results. The first of which is the PREOPANC-2 trial, a multicenter randomized Dutch trial.[16] This follow-up to the PREOPANC trial randomized 375 patients to receive FOLFIRINOX for eight cycles followed by surgery without adjuvant treatment versus three cycles of neoadjuvant gemcitabine with radiation, surgery, and four cycles of adjuvant gemcitabine. At a median follow-up of 41.7 months, median OS was 21.9 months in the FOLFIRINOX arm and 21.3 months in the CRT arm.

RETROSPECTIVE DATA

Given the paucity of randomized data examining neoadjuvant therapy in resectable pancreatic cancer, a multitude of studies have utilized retrospective data to identify the association of neoadjuvant therapy with improved outcomes. Extensive review of the retrospective literature on this topic is beyond the scope of this series; however, a few notable studies are detailed below.

Cass et al. from MD Anderson Cancer Center described their two-decade experience in trends of NT for resectable

PDAC.[17] This retrospective cohort study of 727 patients from 1998 to 2018 showed that 80% of patients in the most contemporary era (2013–2018) received NT with FOLFIRINOX (FFX) or GA. Median OS increased over each era: 30.6 months from 1998 to 2004 (gemcitabine era), 33.6 months from 2005 to 2011 (gemcitabine–cisplatin era), and 48.7 months from 2012 to 2018 (modern FFX or GA era). Postrecurrence overall survival also increased over time over the three 7-year eras (7.8, 12.5, and 12.6 months, respectively) as systemic options increased in effectiveness. On multivariate analysis, neoadjuvant therapy was associated with longer OS.

Sugawara et al. identified patients in the US National Cancer Database with clinical T1 or T2 disease from 2010 to 2017, using a propensity score analysis to compare overall survival between neoadjuvant therapy and upfront surgery, with a landmark analysis of 6 months to accommodate for immortal time bias.[18] A total of 4041 patients received upfront surgery and 933 received multiagent neoadjuvant therapy, reflecting national trends favoring upfront surgery. Median OS was observed to be longer in the multiagent neoadjuvant group compared with upfront surgery (35.9 versus 29.3 months, $p = 0.002$) in a matched cohort.

Stoop conducted a retrospective study including 935 patients who underwent resection for localized PDAC following 2–6 months of initial chemotherapy with either (m) FOLFIRINOX (65%) or gemcitabine–nab-paclitaxel (35%) between 2010 and 2018 across 16 centers in eight countries.[19] The median OS was 43 months (95% CI 38–49) in patients treated with preoperative (m)FOLFIRINOX compared with 36 months (95% CI 31–48) in those treated with preoperative gemcitabine–nab-paclitaxel ($p = 0.16$). Multivariable Cox regression, adjusted for clinical confounders at diagnosis, demonstrated no difference in OS between the two regimens (HR: 0.83; 95% CI, 0.64–1.08).

ONGOING PHASE III CLINICAL TRIALS

A total of three phase III RCTs investigating neoadjuvant therapy for patients with resectable PDAC (Table 2) are ongoing. The ALLIANCE A021806 (NCT04340141) is a phase III RCT in the USA and Canada comparing perioperative mFOLFIRINOX (8 neoadjuvant cycles followed by 4 adjuvant cycles) to upfront surgery followed by adjuvant mFOLFIRINOX (12 cycles) in patients with resectable PDAC.[20] The trial aims to enroll 352 patients. Recruitment commenced in July 2020, and as of 1 June 2025, 319 patients have been enrolled.

Similarly, the PREOPANC-3 (NCT04927780) ongoing phase III RCT in the Netherlands and Sweden is also investigating perioperative (8+4 cycles) versus upfront surgery with adjuvant mFOLFIRINOX (12 cycles) in patients with resectable PDAC, with a target enrollment of 378 patients.[21] Recruitment commenced in August 2021, and, as of 1 June 2025, 353 patients have been enrolled.

Both studies are sufficiently powered to detect clinically significant differences in OS, with preliminary results expected in 2026.

The NeoFOL-R (NCT05529940) is a phase III RCT in South Korea comparing perioperative mFOLFIRINOX (6 neoadjuvant cycles followed by 6 adjuvant cycles) or upfront surgery with adjuvant mFOLFIRINOX (12 cycles), with a target enrollment of 609 patients with resectable PDAC. Recruitment commenced in April 2023.

Of note, eligibility criteria for resectability differ between these three trials. The PREOPANC-3 trial utilizes the Dutch Pancreatic Cancer Group (DPCG) criteria, which defines resectable PDAC as ≤ 90 degrees of venous contact and no arterial involvement. By contrast, the ALLIANCE A021806 and NeoFOL-R trials apply the National Comprehensive Cancer Network (NCCN) criteria, permitting up to 180 degrees of venous contact and no arterial involvement.

FUTURE DIRECTIONS

Active phase I and II trials are currently underway to investigate novel neoadjuvant treatment and explore treatment sequencing, early therapy switching, and addition of targeted and immunotherapies, given their promise in other cancer types. Recent studies have focused on targeting specific molecular alterations, such as KRAS mutations, which are present in > 90% of PDAC cases.[22] Adagrasib and sotorasib, both KRAS G12C inhibitors, have shown promise in early-phase trials for patients with PDAC harboring this specific mutation. Poly(ADP-ribose) polymerase (PARP) inhibitors such as olaparib in patients with germline BRCA1/2 mutations have shown promise in the metastatic setting and may have a role in the future in the perioperative setting.[23] The addition of immunotherapy, such as CD40 agonist sotigalimab, in the metastatic setting is ongoing and may have promise in neoadjuvant therapy in the future. Use of novel agents in the neoadjuvant setting allows for a window of opportunity not present with upfront surgery. Additionally, a pilot study at MD Anderson Cancer Center is investigating the potential of fecal microbiota transplantation (FMT) to modulate the tumor microbiome and potentially reverse immunosuppression in patients with resectable PDAC. These findings may help identify additional targeted therapeutics.

CONCLUSIONS

While the putative advantages of NT for resectable PDAC are compelling, its universal adoption remains limited owing to ongoing debates on prospective evidence and implementation challenges. Theoretical advantages of NT

TABLE 2 Ongoing phase III randomized controlled trials investigating neoadjuvant therapy in patients with resectable PDAC

Trial	Country	Intervention	Comparator	Resectability Status	Primary Outcome	Sample Size	Start	Patients Enrolled[a]	Trial Status[b]
ALLIANCE A021806 [20] NCT04340141	USA, Canada	Neoadjuvant mFOLFIRINOX (8 cycles) followed by surgery and adjuvant mFOLFIRINOX (4 cycles)	Upfront surgery with adjuvant mFOLFIRINOX (12 cycles)	Resectable NCCN	OS	352	July, 2020	319	Recruiting
PREOPANC-3 [21] NCT04927780	The Netherlands, Sweden	Neoadjuvant mFOLFIRINOX (8 cycles) followed by surgery and adjuvant mFOLFIRINOX (4 cycles)	Upfront surgery with adjuvant mFOLFIRINOX (12 cycles)	Resectable DPCG	OS	378	August, 2021	353	Recruiting
NeoFOL-R NCT05529940	South Korea	Neoadjuvant mFOLFIRINOX (6 cycles) followed by surgery and adjuvant mFOLFIRINOX (6 cycles)	Upfront surgery with adjuvant mFOLFIRINOX (12 cycles)	Resectable NCCN	2-year OS rate	609	April, 2023	Unknown	Recruiting

[a]Last verified on 1 June 2025

[b]Trial status according to https://clinicaltrials.gov/ last verified on 1 June 2025

DPCG Dutch Pancreatic Cancer Group, *FOLFIRINOX* fluorouracil, leucovorin, irinotecan, and oxaliplatin, *M* modified, *NCCN* National Comprehensive Cancer Network, *OS* overall survival

have been well delineated in the past three decades, including the potential for tumor downstaging, early treatment of micrometastases, and improved chemotherapy delivery rates. However, robust evidence supporting its superiority over the historical usual care of upfront surgery followed by adjuvant therapy is still lacking.

The landscape of treatment for resectable PDAC is evolving, with an increasing trend towards neoadjuvant therapy in clinical practice. While recent phase II RCTs, such as NORPACT-1, SWOG S1505, and NEONAX, have demonstrated the feasibility and safety of neoadjuvant therapy, they have not definitively established survival benefits compared with upfront surgery. It is important to interpret the results of these trials in context, including challenges in chemotherapy completion rates and the lack of standard treatment dosing and duration. The absence of consistent definitions for resectable disease and the lack of stratification by biological or conditional factors in addition to simply using anatomical criteria have further complicated the interpretation of trial results.

It is important to acknowledge the real-world limitations of neoadjuvant therapy, which include the risk of disease progression during treatment precluding surgical attempt, delays in surgical intervention due to complications including biliary infections and chemotherapy-related immunosuppression, challenges in obtaining histological confirmation for treatment initiation, and preserving/improving performance status during chemotherapy. These pragmatic factors may be particularly problematic in settings with limited resources or not used to multidisciplinary communication, and thus, it is simply easier and seemingly more practical to choose upfront surgery and its associated risks.

An additional and often overlooked dimension of the NT debate centers not only on whether to use neoadjuvant therapy, but which regimen to use. This reflects a key criticism of current practice, given the heterogeneity in regimen selection across trials and institutions. Importantly, the PREOPANC-2 and SWOGS1505 trials and the retrospective study by Stoop et al. indicate no clear OS advantage of (m)FOLFIRINOX over gemcitabine-based regimens in the neoadjuvant setting for resectable PDAC. These findings challenge the notion that (m)FOLFIRINOX should be universally considered the superior or default neoadjuvant regimen and support a more nuanced, patient-tailored approach to regimen selection.

Currently, three phase III RCTs (ALLIANCE A021806, PREOPANC-3, and NeoFOL-R) are underway, with the first two at 90% accrual at the time of writing this review, aiming to provide additional evidence regarding the effectiveness of choosing one treatment sequencing paradigm in resectable PDAC. These trials are powered to detect clinically significant differences in OS, with results eagerly anticipated to guide future treatment strategies. With the current available evidence, the decision to pursue NT or upfront surgery should be made with careful consideration of individual patient factors and institutional expertise. This recommendation will likely persist regardless of the final outcomes of the pending phase III RCT's—the individual assessment of the ABC's of a patient's PDAC is still required to choose the better treatment sequencing for that single patient. As the field progresses, future directions in neoadjuvant therapy for resectable PDAC may include the integration of targeted therapies and immunotherapeutic approaches, potentially offering more personalized treatment options. Future research should focus on optimizing patient selection, standardizing treatment protocols, and identifying predictive biomarkers to personalize therapy. As we await results from ongoing trials, a multidisciplinary approach and careful consideration of individual patient factors remain paramount in decision-making for resectable PDAC.

DISCLOSURES The authors declare that they have no conflict of interest.

REFERENCES

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12–49.
2. Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. *JAMA*. 2021;326(9):851–62.
3. Sohal DP, Walsh RM, Ramanathan RK, Khorana AA. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. *J Natl Cancer Inst*. 2014;106(3):dju011.
4. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet*. 2020;395(10242):2008–20.
5. Khorana AA, McKernin SE, Berlin J, Hong TS, Maitra A, Moravek C, et al. Potentially curable pancreatic adenocarcinoma: ASCO clinical practice guideline update. *J Clin Oncol*. 2019;37(23):2082–8.
6. NCCN. National Comprehensive Cancer Network. Pancreatic adenocarcinoma. version 3.2024. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455.
7. Katz MHG, Pisters PWT, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg*. 2008;206(5):833–46.
8. Merkow RP, Bilimoria KY, Tomlinson JS, Paruch JL, Fleming JB, Talamonti MS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg*. 2014;260(2):372–7.
9. Junior PU, e Silva DD, de Castro N, da Silva Victor E, Rother E, Araújo S, et al. Does neoadjuvant treatment in resectable pancreatic cancer improve overall survival? A systematic review and meta-analysis of randomized controlled trials. *ESMO Open*. 2023;8(1):100771.
10. Patel SH, Katz MHG, Ahmad SA. The landmark series: preoperative therapy for pancreatic cancer. *Ann Surg Oncol*. 2021;28(8):4104–29.
11. Labori KJ, Bratlie SO, Andersson B, Angelsen J-H, Biörserud C, Björnsson B, et al. Neoadjuvant FOLFIRINOX versus upfront surgery for resectable pancreatic head cancer (NORPACT-1):

a multicentre, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2024;9(3):205–17.
12. Schwarz L, Bachet J-B, Meurisse A, Bouché O, Assenat E, Piessen G, et al. Neoadjuvant FOLF (IRIN) OX chemotherapy for resectable pancreatic adenocarcinoma: a multicenter randomized noncomparative Phase II trial (PANACHE01 FRENCH08 PRODIGE48 study). *J Clin Oncol*. 2025:JCO-24-01378.
13. Sohal DPS, Duong M, Ahmad SA, Gandhi NS, Beg MS, Wang-Gillam A, et al. Efficacy of perioperative chemotherapy for resectable pancreatic adenocarcinoma: a phase 2 randomized clinical trial. *JAMA Oncol*. 2021;7(3):421–7.
14. Seufferlein T, Uhl W, Kornmann M, Algül H, Friess H, König A, et al. Perioperative or only adjuvant gemcitabine plus nab-paclitaxel for resectable pancreatic cancer (NEONAX)—a randomized phase II trial of the AIO pancreatic cancer group. *Ann Oncol*. 2023;34(1):91–100.
15. Unno M, Motoi F, Matsuyama Y, Satoi S, Toyama H, Matsumoto I, et al. Neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer: results of the randomized Phase II/III Prep-02/JSAP05 Trial. LWW.
16. Groot Koerkamp B. Neoadjuvant chemotherapy with FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy for borderline resectable and resectable pancreatic cancer (PREOPANC-2): a multicenter randomized controlled trial. ESMO Conference; Madrid, Spain, 2023.
17. Cass SH, Tzeng CD, Prakash LR, Maxwell J, Snyder RA, Kim MP, et al. Trends over time in recurrence patterns and survival outcomes after neoadjuvant therapy and surgery for pancreatic cancer. *Ann Surg*. 2024. https://doi.org/10.1097/SLA.0000000000006269.
18. Sugawara T, Rodriguez Franco S, Sherman S, Torphy RJ, Colborn K, Franklin O, et al. Neoadjuvant chemotherapy versus upfront surgery for resectable pancreatic adenocarcinoma: an updated nationwide study. *Ann Surg*. 2024;279(2):331–9.
19. Stoop TF, Wu YH, Oba A, Ali M, Feld IM, Al-Musawi MH, et al. Survival after neoadjuvant and induction FOLFIRINOX versus gemcitabine-nab-paclitaxel in patients with resected localised pancreatic adenocarcinoma: an international multicentre study. *Br J Cancer*. 2025. https://doi.org/10.1038/s41416-025-03025-1.
20. Chawla A, Shi Q, Ko AH, Beg S, Varghese AM, Behrman SW, et al. Alliance A021806: a phase III trial evaluating perioperative versus adjuvant therapy for resectable pancreatic cancer. *Am Soc Clin Oncol*. 2023;41:TPS4204.
21. van Dam JL, Verkolf EMM, Dekker EN, Bonsing BA, Bratlie SO, Brosens LAA, et al. Perioperative or adjuvant mFOLFIRINOX for resectable pancreatic cancer (PREOPANC-3): study protocol for a multicenter randomized controlled trial. *BMC Cancer*. 2023;23(1):728.
22. Varghese AM, Perry MA, Chou JF, Nandakumar S, Muldoon D, Erakky A, et al. Clinicogenomic landscape of pancreatic adenocarcinoma identifies KRAS mutant dosage as prognostic of overall survival. *Nat Med*. 2025;31:466–77.
23. Kindler HL, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Overall survival results from the POLO trial: a phase III study of active maintenance olaparib versus placebo for germline BRCA-mutated metastatic pancreatic cancer. *J Clin Oncol*. 2022;40(34):3929–39.
24. Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. *Ann Surg Oncol*. 2007;14(7):2088–96.
25. Golcher H, Brunner TB, Witzigmann H, Marti L, Bechstein WO, Bruns C, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. *Strahlenther Onkol*. 2015;191(1):7–16.
26. Casadei R, Di Marco M, Ricci C, Santini D, Serra C, Calculli L, et al. Neoadjuvant chemoradiotherapy and surgery versus surgery alone in resectable pancreatic cancer: a single-center prospective, randomized, controlled trial which failed to achieve accrual targets. *J Gastrointest Surg*. 2015;19(10):1802–12.
27. Reni M, Balzano G, Zanon S, Zerbi A, Rimassa L, Castoldi R, et al. Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2–3 trial. *Lancet Gastroenterol Hepatol*. 2018;3(6):413–23.
28. Versteijne E, van Dam JL, Suker M, Janssen QP, Groothuis K, Akkermans-Vogelaar JM, et al. Neoadjuvant chemoradiotherapy versus upfront surgery for resectable and borderline resectable pancreatic cancer: long-term results of the Dutch randomized PREOPANC trial. *J Clin Oncol*. 2022;40(11):1220–30.